Risk of intracranial hypertension with intrauterine levonorgestrel

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I am concerned about the erroneous and misleading conclusions expressed by Etminan and colleagues in their article published in the June 2015 Issue of *Therapeutic Advances in Drug Safety* [Etminan *et al*. 2015]. There are significant methodological flaws with this study that preclude accurate statistical analysis and interpretation of the data.

The authors used a national database (the United States Food and Drug Administration's Adverse Events reporting system) to determine whether or not there was a statistically significant relationship between the use of Mirena™ and the development of intracranial hypertension, specifically the pseudotumor cerebri syndrome (PTCS). They used several search terms in addition to benign intracranial hypertension, and idiopathic intracranial hypertension (which have identical coding nomenclature), including medical diagnoses that are nonspecific and often relate to other disorders, apart from PTCS. One of the search terms used was cerebral edema. There is absolutely no histological evidence that cerebral edema occurs in PTCS and the conditions producing cerebral edema are, by definition, not PTCS. Disorders causing cerebral edema and intracranial hypertension, such as brain tumors, strokes, trauma, intracranial hemorrhage, hypoxic injury and infection are much more common than PTCS and including these diagnoses in the analysis skews the findings and biases the analysis. Papilledema is also a nonspecific term, coded by physicians to include all etiologies of optic disc edema and is not useful in this context to indicate optic disc edema caused by increased intracranial pressure. Even benign or idiopathic intracranial hypertension, a seemingly distinct and accurate diagnosis, cannot be relied upon to be correct in the context of medical coding with a 50% inaccuracy rate in our series in which medical records were reviewed [Koerner and Friedman, 2014].

The second part of the analysis used a retrospective cohort comparing the risk of PTCS with Mirena™ compared with two other combination oral contraceptives in a large health claims database. They included claims data on women aged 15 to 45 years who were newly prescribed any of the three aforementioned hormonal contraceptives between 2009 and 2013 and analyzed the database for medical events that occurred up to 2012. Prescriptions written after 2012 are obviously irrelevant to events that occurred before a patient ever took the medications being studied. They do not indicate whether they ensured that the medical events had developed during the period between 2009 and 2012; existing, chronic, and unrelated conditions would typically be included in a large claims database. The authors did not ascertain how long women used the contraceptives during the period between 2009 and 2012, as they may have been discontinued after a brief period of time or before the disorder causing intracranial hypertension developed. Moreover, Mirena™ is an implantable intrauterine delivery system that may be left *in situ* for up to 5 years. A Mirena™ device inserted at the end of the study period cannot be considered with equivalency to a device implanted earlier in the study time frame. There are likely many women included in the database who were using either the oral contraceptives or Mirena™ and were not captured because medication was prescribed before 2009, yet the patients remained on the treatment of interest. Search terms for this analysis were even more egregious than in the first methodology, including obstructive hydrocephalus as well as cerebral edema, conditions which are unrelated to using hormonal contraceptives and distinct entities from PTCS.

It should be noted that one condition associated with oral contraceptive use is cerebral venous sinus thrombosis, which may cause a syndrome identical to PTCS in phenotype. The authors did not

consider this confounding variable when searching for women who had papilledema, benign intracranial hypertension or cerebral edema. Their analysis likely included some patients with cerebral venous sinus thrombosis, which produces intracranial hypertension but is a distinct entity from PTCS.

The authors failed to include a control group of women who were not using the hormonal contraceptives of interest, or any hormonal contraceptive at all. They state that there was no statistically significant difference in the development of 'intracranial hypertension' (arising from distinct and unrelated conditions) between users of two oral contraceptives and Mirena™ but do not assess whether or not the rate is higher than would be expected in their population sample in general. It is inappropriate to use historical control data for the prevalence of idiopathic intracranial hypertension (10 to 20 per 100,000 in the demographic at highest risk) as a comparator in this study that included other diagnoses that occur at a much higher prevalence.

There is no published evidence substantiating a causal relationship between PTCS and hormonal contraception [Digre and Corbett 2001; Ireland *et al*. 1990]. The patient described in the case report cited by the authors [Martinez *et al*. 2010] did not meet the diagnostic criteria for PTCS.

Finally, the authors did not disclose a major and relevant conflict of interest. The lead author of the paper has been retained as a medical expert for a lawsuit against Bayer by the plaintiff's attorney who is suing the company for alleged cases of PTCS related to Mirena™ use. I am aware of this because of a personal communication that I received from Dr Etminan prior to the publication of this article. I was invited by the journal to review the manuscript for publication but declined, indicating that I have been retained by Bayer as a medical expert and that being a reviewer was a conflict of interest for me.

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